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THE OXYGEN DEFICIENCY TEST. PRINCIPLES AND RELATIONSHIPS TO REGULATIVE PROCESSES IN THE ORGANISM.

H. Brüner, K. Dietmann and K. E. Klein

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Systematic investigations of the efficiency deterioration in a defined oxygen deficiency ("altitude position experiment") for a large group of subjects, and mathematical evaluation of the results permit the plotting of a typical, mean deterioration curve and - via a frequency distribution of the end of efficiency - the establishment of two groups, A and B, with different behavior in oxygen deficiency. The "critical threshold" is reached, according to these findings, only after twice the time previously assumed. The mean terminal efficiency and the duration of efficiency have characteristic age curves: both increase up to age 50. Disturbances to autonomic nervous functions behave inversely to the age curves of the mean terminal efficiency. Another striking relationship exists between posthypoxic eosinopenia and the two groups, A and B. The correlations demonstrated indicate further testing of the so-called "functional efficiency reserve".

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Author

As a result of intensive altitude research during the past four decades and numerous special patho-physiological investigations, we are today extensively oriented on the effects of acute inspiratory oxygen deficiency. The symptomatics of the altitude rise test (continual or step-wise decrease in inspiratory pO_2) or the altitude position test (sudden change from breathing air or oxygen to a firm, lowered, inspiratory pO_2) have been described in detail by Henderson [12], Schneider [18], Barcroft [2, 3], Strughold [19, 20], Hartmann [10], Benzinger [4, 5], Armstrong [1], Opitz [15], et al.

Systematic investigations of oxygen deficiency in a group of over 3,000 persons from 17 to 50 years of age gave us cause to report some new points of view on the methods of the altitude position test (ball test process) in an earlier publication [7], and at the same time to point out that the deteriora-

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*/Numbers in the margin indicate pagination of the original foreign text.

tion of central somatic and autonomic nervous functions in oxygen deficiency does not by any means take place according to a relatively rigid pattern in all test persons.

At this point, our previous observations should be supplemented, defined and statistically assured. We should also investigate what possible perspectives, in regard to a general performance test, are opened by individual testing of the performance deterioration in defined, acute inspiratory oxygen deficiency, beyond the determination of oxygen deficiency tolerance.

METHODICS

I. We have already reported on the methodics of the oxygen deficiency experiment on which these results are based [6, 7], and also on the evaluation of the ball test. We now examined two groups of 200 and 250 persons ranging in age from 17 to 50 during the periods 1957/58 and 1958/59. Selection was made /2 only with a view to obtaining a uniform distribution in all age groups. The investigations were thus conducted under oxygen deficiency conditions which corresponded exactly enough to a sudden inspiratory oxygen content of 7 vol.-% (= 50.4 mm Hg O_2 partial pressure). Two criteria can be valid for the definition of the end of the experiment:

1. The decline of the ball efficiency to 0% and

2. the loss of spinal and central control of muscle tonus as evidenced by loss of reflexes.

The subject "tips" from the chair. This latter criterior for the "critical threshold" seems to us sharper than the loss of consciousness chosen by Strughold [19, 20].

II. Neuroautonomic symptoms were determined in the internal, or neurological

pre-examination by specialists who were unaware that there would be a subsequent evaluation of the findings in relationship to the oxygen deficiency test. Thus there is no subjective underevaluation or overevaluation of these purely clinical findings.

III. The counting of eosinophils was done in strict accordance with the first method of direct counting given by Thorn [22]. Blood samples were taken shortly before and in the 1st, 2nd, 3rd and 4th hours after the oxygen deficiency test. Modifying Thorn's procedure, we took the blood from the finger. Counting was done immediately after preparation of the blood and the average was computed from four counting chambers. Strict abstinence from food was demanded of the subjects during the conduct of the investigation.

IV. In the mathematical treatment of our results, particularly in testing significance, we employed the customary methods (zero hypothesis) for computing the arithmetic mean = x, the mean deviation (standard deviation) = s and the probability P.

RESULTS

1. The mean efficiency deterioration in oxygen deficiency, determined with the ball test process, follows the course of the curve shown in Figure 1 - without regard to different age groups. Reaction threshold, disturbance threshold and time reserve generally agree with the values previously published by Strughold [19, 20] for 7,500 m altitude INA. Strughold reports an average 6.5 min. for the so-called "critical threshold" (Figure 1). The "critical threshold" according to Strughold means the loss of consciousness, possibly the beginning of convulsions. Even with broad interpretation of these symptoms, we are unable to determine the occurrence of the "critical threshold" before the 11th

minute on the average. With very critical evaluation, employing our own definition given in the methodics, the critical threshold may, on the average, be reached only at a considerably later time. Naturally, no exact data can be given on the length of the so-called "remaining time" (i.e., the time from the critical threshold to death from oxygen deficiency) for humans. The average course of deterioration in Figure 1 again elucidates the observation [7] that, as a rule, decisive changes or permutations in the reactions of the organism occur in the 3rd, 4th and 5th minute. As is to be expected, this "critical /3 deterioration" (steeply declining section of curve) occurs at different times depending on the individual.

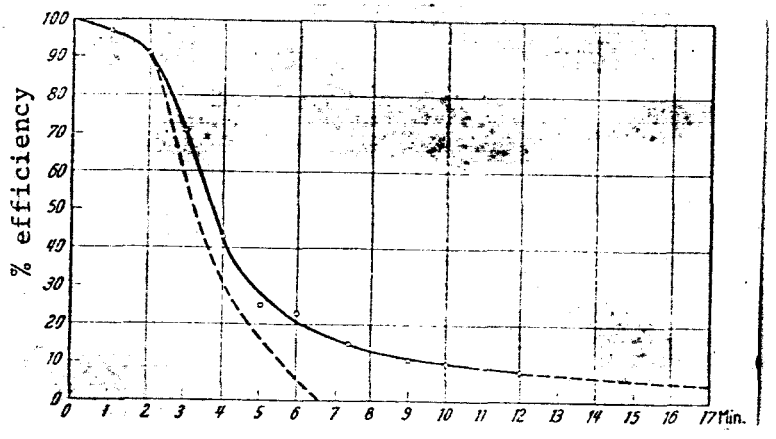


Figure 1. Mean efficiency deterioration in acute hypoxia (P_{O_2} insp. 50.4 mm Hg) N = 200. The broken curve represents the reconstructed deterioration according to Strughold.

2. As already reported [6, 7], observation of a large number of subjects in the oxygen deficiency test led us to the empirical formulation of two characteristic reaction types: type A with brief, rapidly failing efficiency, and type B with efficiency deterioration which lasts longer and exhibits an asymptotic course. If this observation is correct, it must be detectable in a fre-

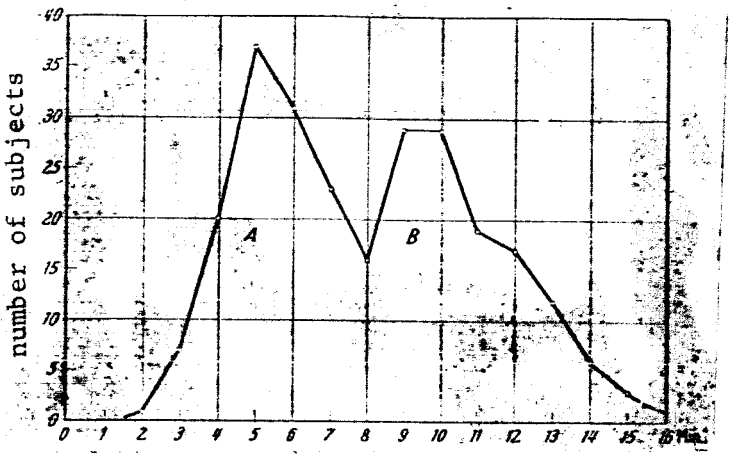


Figure 2. Frequency distribution of efficiency limit in acute hypoxia (P_{O_2} insp. 50.4 mm Hg) N = 250.

quency distribution of the efficiency limit. Figure 2 provides this proof. /4 The probability that the polygonal figure represents two separate groups of approximately normal distribution is very great. On the other hand, it is very improbable that Figure 2 involves the distribution of a homogeneous group. The two groups merge in the eighth minute. For reasons to be discussed later, such an overlapping is also to be expected.

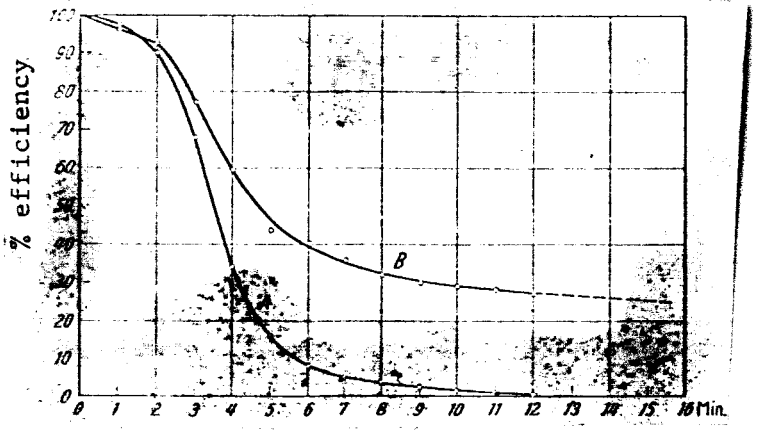


Figure 3. Mean efficiency deterioration of groups A and B in acute hypoxia (P_{O_2} insp. 50.4 mm Hg) N = 200.

3. With the frequency distribution of Figure 2, the two groups, A and B,

TABLE 1 (TO FIGURE 3). MEAN EFFICIENCY DETERIORATION OF GROUPS A AND B IN ACUTE HYPOXIA.

	A			B	
minute	$\bar{x}$	s	P	s	$\bar{x}$
1	97.4	10.6	$< 3 \cdot 10^{-1}$	7.6	96.0
2	89.9	13.1	$< 9 \cdot 10^{-2}$	12.6	93.2
3	68.2	30.4	$< 10^{-2}$	18.6	77.9
4	34.4	25.0	$< 10^{-9}$	21.0	58.8
5	16.1	17.4	$< 10^{-9}$	21.4	44.2
6	7.7	12.0	$< 10^{-9}$	21.3	46.4
7	4.9	9.3	$< 10^{-9}$	20.3	35.9
8	3.4	9.4	$< 10^{-9}$	20.7	32.3
9	2.1	7.9	$< 10^{-9}$	18.6	30.0
10	0.9	5.8	$< 10^{-9}$	19.4	29.3
11	0.3	3.2	$< 10^{-9}$	15.8	27.8
12	-	-	-	18.9	26.0

are proved with great probability and approximately defined. They can now be further analyzed comparatively. The first point of interest is the mean efficiency deterioration of each of the two groups, as presented in Figure 3. /5 The efficiency values differ significantly from each other even from the third minute on (Table 1). The so-called "critical deterioration" in group A quickly leads to absolute inefficiency and to rapid attainment of the so-called "critical threshold". On the other hand, the "critical deterioration" in group B is followed by a more or less strongly pronounced compensation phase which manifests itself in an efficiency level which slowly, asymptotically drops toward zero.

This compensation process can sometimes be seen directly in the course of the deterioration curve. A transitory increase of efficiency by 20-30% follows after the "critical deterioration".

4. The basic criteria which determine the group to which a subject belongs are the time of the end of efficiency (ball efficiency approximately zero) and

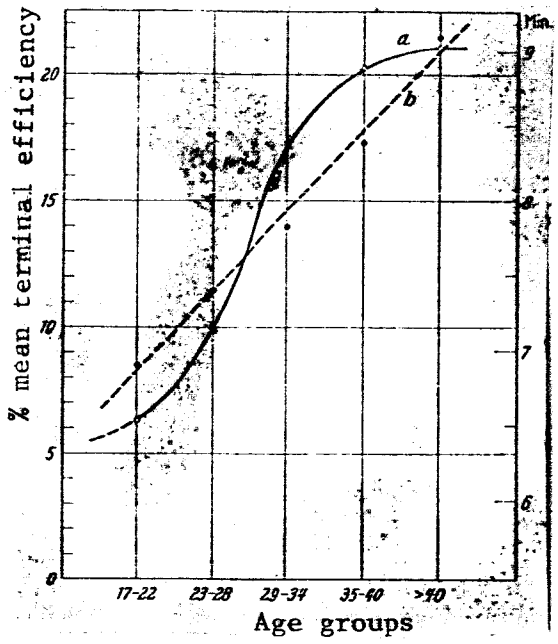


Figure 4. Age variation of the mean terminal efficiency (a) and of the end of efficiency (b) in acute hypoxia (P_{O_2} insp. 50.4 mm Hg).

the mean efficiency, particularly the mean terminal efficiency, i.e., the efficiency after the "critical deterioration". Previous observations had already shown that age is obviously a factor of these criteria. Figure 4 shows an analysis of this age dependence.

TABLE 2 (TO FIGURE 4). AGE VARIATION OF THE MEAN TERMINAL EFFICIENCY AND OF THE END OF EFFICIENCY IN ACUTE HYPOXIA.

	17-22			> 41	
Age groups	$\bar{x}$	s	P	s	$\bar{x}$
Mean terminal efficiency (percent)	6.3	11.9	$< 10^{-9}$	25.0	21.1
End of efficiency (min.)	6.9	3.1	$< 10^{-3}$	2.8	9.1

These two criteria assume higher values with increasing age with a certain regularity, i.e., in the age group we investigated, the mean terminal efficiency and the absolute duration of the test improve with older age. The variation of end of efficiency (time) describes an approximately straight line; that of mean terminal efficiency, a hyperbole. Schwarz [20] found a similar age dependence for the time reserve in climbing experiments. The values of the extreme age groups are significantly different for the mean terminal efficiency and for the end of efficiency (Table 2). /6

5. After determination of the age deviation of O_2 deficiency resistance, it seemed advisable to look for age dependence of other biological magnitudes or changes. Geriatric research offered a wealth of material from which we first selected autonomic-nervous functional disturbances (Curtius et al. [8, 9]) for reasons of methodology.

From the internal and neurological findings, the following were recorded as symptoms of autonomic-nervous functional disorders (see also methodology):

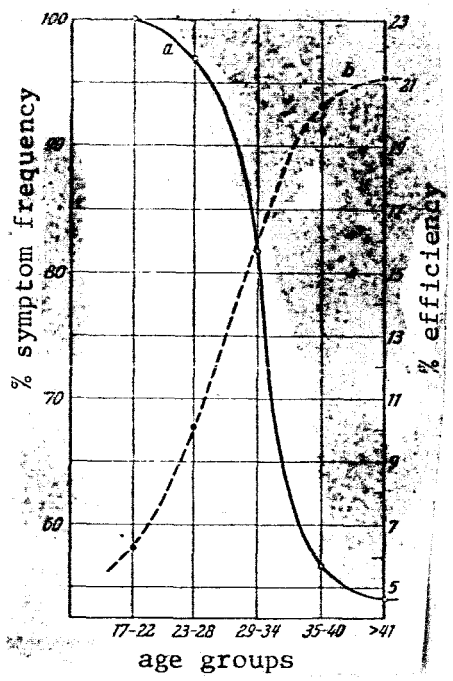


Figure 5. Age deviation of autonomic nervous functional disturbances (a) in comparison with age deviation of mean terminal efficiency (b) in acute hypoxia (P_{O_2} insp. 50.4 mm Hg).

respiratory arhythmia, eretic functioning, pronounced dermographia, hyperhidrosis, Chvostek's symptom, tremor, lid flutter, increased patellar tendon reflex. For every age group the symptom frequency was computed, the initial value of the youngest group was set = 100%, and the course for the other age groups was expressed in a percentage based on the 100% of the youngest age group (Figure 5).

TABLE 3 (TO FIGURE 5). AGE DEVIATION OF AUTONOMIC NERVOUS FUNCTIONAL DISORDERS.

	17-22			> 41	
Age groups	$\bar{x}$	s	P	s	$\bar{x}$
Symptom frequency	2.49	1.4	$< 10^{-9}$	1.2	1.33
In percent	100	-	-	-	53

From Figure 5 it can be seen that the autonomic-nervous functional dis- /7

turbances become less with increasing age after a peak in the early twenties. The age curve therefore runs in an opposite manner from that of the mean efficiency, i.e., the more pronounced the autonomic-nervous functional disorders in a subject, the less his efficiency in the oxygen deficiency test.

6. If we proceed from the idea that the oxygen deficiency represents an unspecific stress reaction in the body (von Muralt [14], Brüner and Dietmann [7], Schäfer [16]), then, based on the concepts of the stress mechanism (Selye [17], Thorn [22]), a change in the eosinophile leukocyte count in the blood stream must be detected. Therefore, observing the precautions for the Thorn test (see methodology), we conducted counts of the eosinophils up to four hours after the oxygen deficiency and compared them to the initial values. The results are shown in Figure 6. There is a marked drop in eosinophils with a low point in the third hour after oxygen deficiency. The drop is clearly greater for the subjects of group A than for those of group B. The differences in the

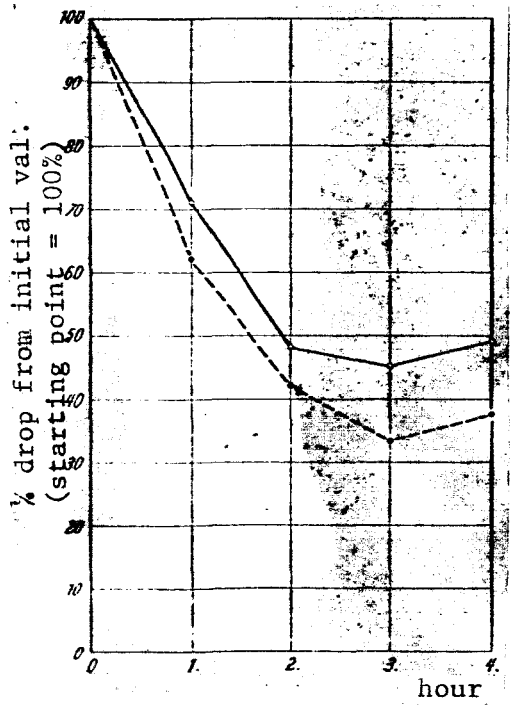


Figure 6. Decrease of eosinophils in the blood after acute hypoxia (P_{O_2} insp. 50.4 mm Hg).

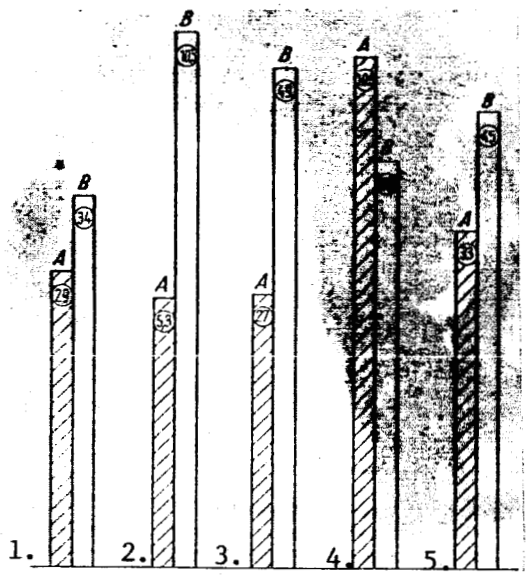
percent decrease for the third and fourth hours are significant (Table 4).

TABLE 4 (TO FIGURE 6). DECREASE OF EOSINOPHILS IN THE BLOOD AFTER ACUTE HYPOXIA.

Group decrease in the	A			B	
	$\bar{x}$	s	P	s	$\bar{x}$
1st hour	62.3	20.2	$< 3 \cdot 10^{-1}$	13.6	71.5
2nd hour	42.2	16.2	$< 3 \cdot 10^{-1}$	12.7	47.0
3rd hour	32.8	13.6	$< 10^{-2}$	12.0	44.7
4th hour	37.8	19.2	$< 5 \cdot 10^{-2}$	21.8	51.3

The different stress effect is expressed even more clearly when a group /8 of subjects is subjected to oxygen deficiency for an equally long period of time. We subjected each subject of a small group to a hypoxia of 50.4 mm Hg insp. for five minutes and then compared the eosinophils with the initial values up to 4 hours. The regular oxygen deficiency test was conducted thereafter and used to determine the group to which the subject belonged. This showed a more clearly marked difference between short and long duration of experiments, i.e., between groups A and B. The decrease for the B types averaged only 30%; for the A types, over 70%.

7. Several basic findings for both A and B groups are again compared in Figure 7. As is to be expected on the basis of the age curves for mean efficiency and duration of experiment, the mean age of group B is higher. The mean experiment duration is computed from the frequency distribution (Figure 2) of both groups; the mean total efficiency, from the deterioration curves of /9 Figure 3. The symptom frequency of neuro-autonomic functional disturbances of group A was set = 100%. In comparison, 80% (symptom frequency) was computed for group B. The eosinophils drop on the average to 33% of the initial value



KEY: 1 - average age. 2 - mean time (duration of experiment) in min. 3 - mean total efficiency in %. 4 - disorders of neuro-autonomic functions. 5 - decline in eosinophils in the 3 hours after hypoxia as % of initial value.

Figure 7. Synopsis of groups A and B according to their behavior in acute hypoxia (P_{O_2} insp. 50.4 mm Hg).

TABLE 5 (TO FIGURE 7). SYNOPSIS OF GROUPS A AND B.

		$\bar{x}$	s	P
average age of the group	A	29.2	9.1	$< 10^{-4}$
	B	34.0	9.2	
mean time in minutes	A	5.3	3.1	$< 10^{-9}$
	B	10.5	1.8	
mean total efficiency	A	27.1	38.2	$< 10^{-9}$
	B	49.3	30.8	
disorders of neuro-autonomic functions (symptom frequency)		2.35 (100%)	1.36	$< 10^{-3}$
		1.90 (80%)	1.68	
Percent decrease in eosinophils in the third hour	A	32.8	13.5	$< 10^{-2}$
	B	44.7	12.0	

for group A; to 45% for group B. The computation of significance for the differences between groups A and B can be seen in Table 5.

DISCUSSION OF RESULTS

An exact, typical, individual curve, the course of which indicates the deterioration of central autonomic and somatic nervous regulations, can be derived in the so-called "altitude position test" at 7,500 m (corresponding to an insp. O_2 partial pressure of 50.4 mm Hg at 100% humidity and 37°C) with the ball test process. Data reported previously on the "stimulus thresholds" and the "time reserve" are confirmed. On the other hand, we must correct the time given for the "critical threshold". According to our findings, it occurs after the 12th minute, i.e., twice as late as previously reported (6.5 minutes according to Strughold [19, 20], Figure 1). A possible practical interpretation of this finding for flight medicine will not be discussed here.

The concept of two different reaction types in oxygen deficiency, which we derived empirically, was mathematically-graphically defined and confirmed by statistical methods (Figure 2). Both reaction types occur in all age groups, but not uniformly distributed. The A types predominate in the younger groups (10 to 30); the B types, in the older. The transition lies between 25 and 35. It can be seen from the overlapping of the frequency distribution and from the steep portion of the age curve for mean efficiency (Figure 4).

In a careful study of literature, we came across studies by Schneider and Lutz [18, 13] from 1919-1921, in which the authors reported similar observations with reference to our two groups or reaction types A and B. Schneider and Lutz report a ratio of 46:54 for "fainters" and "non-fainters". By "fainters" they understood subjects who, after a relatively brief oxygen insufficiency and

as a result of primary failure of respiration and circulation, suffered a more or less pronounced collapse, while the "non-fainters", with adequate respiratory and circulatory regulation, slowly lost consciousness at a later time as a result of the cerebral effects of hypoxia. Although this report is mentioned by Strughold [19] and by Armstrong [1], no practical conclusions were ever drawn from it. We have no doubt that our A and B groups are approximately identical with the "fainters" and "non-fainters" of Lutz and Schneider. /10 However, we are of the opinion that the causes of the early, relatively abrupt failure of the A types, or "fainters", are not to be found, at least not exclusively, in a primarily poor regulation of respiration and circulation. We will discuss this very interesting question and present experimental results in a later publication.

The reactive behavior in a defined oxygen deficiency - i.e., the deterioration curve determined by us - can be viewed as specific reaction to hypoxia. Under these circumstances, the test results would permit only a statement on oxygen deficiency tolerance. We know with a good degree of certainty that the functional proficiency of cerebral centers is dependent on partial oxygen pressure in the cerebral capillaries and in the venous capillary peduncle. With constant inspiratory oxygen pressure, the oxygen tension on the venous side of the central circulation is the resultant of numerous individual factors, which can be represented with sufficient accuracy by the following main components:

1. the pressure drop of the oxygen from the inspired air to the arterial blood,
2. circulatory volume per minute,
3. regulation of blood distribution,
4. central oxygen consumption,

5. respiratory quotient,

6. oxygen capacity of the blood,

7. binding capacity of the carbon dioxide in the blood (alkali reserve).

All components named can become limiting for a definite oxygen deficiency resistance either isolated or, what is much more probable by their close regulative connection, combined. On the other hand, however, the functional proficiency of these components or their good regulatory interaction, is a decisive condition for a good functional efficiency of the organism. Functional weaknesses in efficiency, which produces a lessened oxygen deficiency resistance, will have an unfavorable effect with all other stresses on these regulation systems. This furnishes the first basis for our concept that not only is the oxygen deficiency tolerance a specific magnitude, but it also permits an extensive statement concerning the functional proficiency of vital regulation systems.

This concept receives considerable support from the behavior of the eosinophile leukocytes after acute hypoxia of sufficient intensity. The oxygen deficiency apparently evokes a typical stress situation, the effects of which - seen for example in the decline of eosinophils - can be correlated with the extent of the oxygen deficiency tolerance (Figure 6). With a stimulus of /11 equal magnitude (5 mins. O_2 deficiency) for all subjects, the response is considerably greater for the A types. The same "stessor" causes a greater stress. The quantitative differences of unspecific stress reactions, for the same stimulus, which vary with the individual and are sometimes quite large (Selye [17]), may possibly thus be made accessible to a direct quantitative analysis.

Finally, the systematic investigation of disturbances to autonomic nervous functions in our subjects leads to the striking result that the mean efficiency

increases as the symptoms decrease (Figure 5). Here, too, the conclusion can be drawn that disorders in autonomic regulation can be correlated to a reduced resistance to oxygen deficiency, and that, on the other hand, stable autonomic functioning is linked to a high resistance to oxygen deficiency or mean efficiency in oxygen deficiency.

The problem of oxygen deficiency as a test to determine the functional soundness of vitally important regulation systems ("functional capacity reserve") has not been treated exhaustively with these remarks. Moreover, the questions raised by this study were intended only to point out the possible perspectives of the problem. In a future publication we shall attempt, on the basis of experimental results - some not yet published - to present a detailed justification of our concept of the applicability of the oxygen deficiency test for studying the human "functional efficiency reserve".

SUMMARY

Systematic investigations of the efficiency deterioration in a defined oxygen deficiency ("altitude position experiment") for a large group of subjects, and mathematical evaluation of the results permit the plotting of a typical, mean deterioration curve and - via a frequency distribution of the end of efficiency - the establishment of two groups, A and B, with different behavior in oxygen deficiency. The so-called "critical threshold" is reached, according to these findings, only after twice the time previously assumed. The mean terminal efficiency and the duration of efficiency have characteristic age curves: both increase up to age 50.

Disturbances to autonomic nervous functions behave inversely to the age curves of the mean terminal efficiency and duration of efficiency. Another

striking relationship exists between the posthypoxic eosinopenia and the two groups, A and B. The oxygen deficiency stress apparently triggers a greater reaction of the hypophysis-adrenal cortex system in the A types than in the B types.

The correlations shown in the comparison of disturbances in autonomic /12 nervous functions with mean efficiency, and of posthypoxic eosinopenia with the reaction types open concrete perspectives for a testing of the so-called "functional efficiency reserve".

REFERENCES

1. Armstrong, H. C.: Principles of Aviation Medicine (Monograph) London, 1939.
2. Barcroft, J.: The respiratory function of the blood (Die Atmungsfunktion des Blutes) (Monograph) I Berlin: Springer, 1927.
3. Barcroft, J.: The respiratory function of the blood (Die Atmingsfunktion des Blutes) (Monograph) II Berlin: Springer, 1929.
4. Benzinger, Th.: Naturwissenschaften 28: 209, 1940.
5. Luftfahrtmedizin 1: 326, 1937.
6. Brüner, H.: DVL Report (symposium on questions of flight medicine. Bad Godesberg) (DVL-Bericht Symposium ü. flugmediz. Fragen. Bad Godesberg) 30/31 October 1956.
7. Brüner, H., and K. Dietmann: Int. Z. angew. Physiol. 17: 190-206, 1958.
8. Catsch, A., and H. Ostrowski: Z. menschl. Vererb.- u. Konstit.-Lehre 26, 1942.
9. Curtius, F.: In: Handbook of Internal Medicine (Hdb. d. Inn. Med.) VI/1, p. 213 ff., Berlin-Göttingen-Heidelberg: Springer, 1954.
10. Hartmann, H.: Luftfahrtmedizin 1: 1-14, 1936.
11. Hartmann, H.: Luftfahrtmedizin (proceedings), 1: 44, 1936/37.
12. Henderson, Y.: J. biol. Chem. 43: 29, 1920.
13. Lutz, B. R., and E. C. Schneider: Amer. J. Physiol. 1: 228, 280, 327, 1919.
14. Muralt, A. v.: In: Handbook of Internal Medicine (Hdb. d. Inn. Med.), VI/2, p. 258 ff., Berlin-Göttingen-Heidelberg: Springer, 1954.
15. Opitz, E.: Ergebn. Physiol. 44: 315, 1941.
16. Schäfer, G.: Int. Rdsch. Physik. Mediz. 11: 4, 1958.
17. Selye, H.: The Physiology and Pathology of Exposure to Stress (Monograph) Montreal, 1950.
18. Schneider, E. C.: Physiol. Rev. 1: 631, 1921.

REFERENCES

19. Strughold, H.: Luftfahrtmedizin 5: 1, 1940.

20. Dtsch. Milarzt 1: 1, 1936.

21. Schwarz, W.: Luftfahrtmedizin 1: 39, 1936.

22. Thorn, S. W.: Adrenal Cortex Insufficiency (Nebenniereninsuffizienz) (Monograph). Bern-Stuttgart: Huber, 1953.

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